REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

In the specification, a paragraph has been added on page 1. The amendment identifies a related application.

Claims 11, 15, 21-27, 30-32, 34, 37-40, and 44 are currently being amended. The amendments to all but claim 22 are made to correct minor typographical errors. Claim 22 has been amended, as discussed below in Section IV. Support for these amendments can be found throughout the specification as filed, including the original claims and pages 34-35 of the specification.

Claims 47-51 are being added. Support for these claims can be found throughout the specification as-filed, including the original claims and page 39 of the specification.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested. After amending the claims as set forth above, claims 1-51 are now pending in this application, and claims 8, 10-16, 30, 32-38, and 46 are withdrawn. Thus, claims 1-7, 9, 17-29, 31, and 39-45, and 47-51 are pending and being examined on the merits.

I. Restriction/Election

The Office Action acknowledges Applicant's election of Group III and SEQ ID NO: 1, with traverse. The Office Action also rejoins Groups I, II, and VII for consideration with Group III.

Applicant appreciates the Examiner rejoining Groups I, II, and VII with elected Group III. Applicant notes that claims 1-3, 17-25, and 39-45 are indicated as linking claims and that the restriction requirement will be withdrawn between the linked inventions upon the linking claims being found allowable.

II. Claim Objections

Claim 23 was objected to because it recites 'SEQ ID NO 1' for AD7C-NTP. Office Action at 4. According to the Office Action, the specification was amended such that SEQ ID NO: 1 identifies a nucleic acid molecule and SEQ ID NO: 10 identifies the corresponding amino acid sequence.

Applicant has amended claim 23 to recite "SEQ ID NO: 10" rather than "SEQ ID NO: 1," as suggested by the Office Action. Thus, Applicant respectfully requests withdrawal of this ground of objection.

III. Objections to the Specification

The Office Action objects to the specification because the first line of the application should be updated to indicate the related applications. Applicant has amended the specification to indicate the related application. Thus, Applicant respectfully requests withdrawal of this ground of objection.

IV. Claim Rejections – 35 U.S.C. § 112, Second Paragraph

Claims 22 and 44 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. According to the Office Action, the phrase "the NTP is part of a single new cloned recombinant molecule consisting of NTP and a molecule" renders the claims unclear.

Applicant notes that claim 44 does not recite the phrase "the NTP is part of a single new cloned recombinant molecule consisting of NTP and a molecule," as stated in the Office Action. Thus, it is not clear why claim 44 is rejected. Indeed, claim 44 is clear and definite as currently written. Accordingly, Applicant respectfully requests that the rejection of claim 44 be withdrawn.

While not acquiescing in the propriety of the rejection, Applicant has amended claim 22 to no longer recite the phrase deemed objectionable, thereby rendering the rejection moot. Claim 22 is clear and definite as amended. Thus, Applicant respectfully requests reconsideration and withdrawal of this ground of rejection.

V. Claim Rejections – 35 U.S.C. § 112, ¶ 1 - Enablement

A. Claims 1-7, 9, 17-29, 31, & 39-45

Claims 1-7, 9, 17-29, 31, and 39-45 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. According to the Office Action,

> the specification, while being enabling for a method of treating a benign tumor, a malignant tumor, hyperplasia, hypertrophy, overgrowth of a tissue and malformation of a tissue in a patient requiring removal or destruction of cells comprising locally administering (e.g. topically, intratumorally) to a mammal in need a therapeutically effective amount of the neural thread protein consisting of SEQ ID NO. 10, does not reasonably provide enablement for a method of treating any and all conditions in a patient requiring removal or destruction of cells comprising systemically administering (e.g. intravenously, intra-arterially, intraperitoneally) to a mammal in need a therapeutically effective amount of any and all neural thread protein (NTP) as well as fragments, variant, derivative, homolog, reverse-D peptide, and enantiomers of NTP.

Office Action at 6-7. Applicant respectfully traverses this ground of rejection.

Claims 1-7, 9, 17-29, 31, and 39-45 are enabled, as discussed below. In addition, Applicant has added claims 47-51, which recite subject matter indicated in the Office Action as allowable. Thus, Applicant respectfully requests that claims 47-51 be allowed even if the PTO maintains the rejection of claims 1-7, 9, 17-29, 31, and 39-45 as allegedly lacking enablement.

The specification contains a complete description of the invention of claims 1-7, 9, 17-29, 31, and 39-45 sufficient to allow one of skill in the art to make and use the claimed invention without undue experimentation. The enablement of the claimed invention is discussed below with reference to the factors articulated in *In re Wands*, 8 USPQ.2d 1400 (Fed. Cir. 1988).

1. Nature of the Claimed Invention

Claims 1-7, 9, 17-29, 31, and 39-45 are drawn to a method of treating a condition in a patient requiring removal or destruction of cells. The method comprises "administering to a mammal in need a therapeutically effective amount of a neural thread protein (NTP)." Dependent claims specify particular routes of administration and conditions that can be treated.

2. Breadth of Claims

Claims 1-7, 9, 17-29, 31, and 39-45 are drawn to a "method of treating a condition in a patient requiring removal or destruction of cells comprising administering to a mammal in need a therapeutically effective amount of a neural thread protein (NTP)." Thus, the claims are directed to treating a condition "requiring removal or destruction of cells" comprising administering "NTP" to a mammal. Conditions "requiring removal or destruction of cells" are well-known in the art, and the specification contains an extensive description of such conditions (pgs. 33-34). Similarly, NTPs are well known in the art, as discussed in the specification (*see e.g.*, pgs. 5-6 and 9-11). Finally, the formulation of different dosage forms depending on the particular route of administration are known in the art (*see e.g.*, pgs. 36-41).

3. Level of Ordinary Skill & Predictability in the Art

The biological sciences have been characterized as unpredictable as compared to other technology areas, such as mechanical engineering and electronics. However, the level of ordinary skill in the art is very high with one of ordinary skill in the art typically having an advanced degree and industry experience.

In addition, certain areas of biological science are more predictable than others. For example, the production of biologically active fragments, variants, and derivatives is predictable based on the knowledge of conservative amino acid substitutions (*see e.g.*, pg. 1-1, Tables 1 and 2) and the availability of routine screening methods (*see* examples).

4. The State of the Prior Art & Guidance Provided By The Specification

The prior art contains detailed teachings of NTP and how to make NTP, as summarized on pages 5-6 and 9-11 of the specification. Derivatives, variants, homologs, variants, and other forms of NTP that retain their biological activity can also be made using routine techniques well-known in the prior art (*see e.g.*, 11-18). For example, conservative amino acid substitutions can be made to naturally occurring NTP such that the modified NTP retains biological activity. The specification contains an extensive description of how to make NTP and modified forms thereof with citations to relevant prior art references (*see e.g.*, pgs. 19-32).

Conditions requiring destruction or removal of cells are known in the art and include, for example, cancer, hyperplasia, unwanted hair, and warts (*see e.g.*, pgs. 33-34). These conditions are well-characterized and diagnostic methods are available to identify these conditions. Representative conditions are listed in the specification (*id.*).

The prior art also contains extensive teachings about how to make particular dosage forms depending on the desired routes of administration (*see e.g.*, pgs. 36-41). These teachings include a description of how to conjugate active agents to other molecules to direct the active

agents to a particular site, such as the site of tumor growth (*see e.g.*, pgs. 34-36). For example, active ingredients can be conjugated to antibodies specific for tumor cells (*id.*). By using site-specific conjugates, NTP can be administered systemically but still delivered to the site of the cells requiring removal or destruction. The specification describes various dosage forms, routes of administration and methods of forming compositions comprising NTP, such as NTP-antibody conjugates (*id.*; pgs. 34-36).

The Office Action contends that "the specification fails to teach how to make [NTP conjugates] that [are] tumor- or site specific i.e., the activity of NTPs is shut down or inhibited during delivery and turned on only at required sites." Office Action at 11. However, the specification does describe forming site-specific NTP compositions (pgs. 34-36), and the formation of site-specific compositions is known in the art. For example, chemotherapeutic agents can be delivered as conjugates to make the agents site specific. In addition, antibodies to NTP are known (pg. 10, ¶ (c)), and methods of making antibodies to specific targets are known in the art. Thus, the specification need not describe specific methods of making site-specific NTP conjugates, because a "patent need not teach, and preferably omits, what is well known in the art." MPEP § 2164.01.

5. Working Examples

The teachings of the specification are verified by the working examples. Example 1 demonstrated that an NTP was cytotoxic on glioma and neuroblastoma cells. The results demonstrated that "[s]ignificant cytotoxic effects on glioma and neuroblastoma cells" could be observed at 24 and 96 hours (pg. 45). Example 2 "was to determine the effect of NTP on tissue at sites of injection." Again, "[i]njection of AD7C-NTP in ***all examples*** produced abundant acute necrosis of tissues at the injection sites" (pg. 45 (emphasis added)). Finally, Example 3 "was to determine the effect of NTP on different human and non-human origin tumors." The experiment confirmed that "there was significant necrosis" in "***all cases tested***" (pg. 46 (emphasis added).

The Office Action states that "no working example is provided for a method of treating any other conditions by any other NTP." However, the examples provided are steadfastly consistent. Regardless of the type of tissue or its origin, the NTP induced acute necrosis. Moreover, there is no evidence or explanation to suggest that NTPs other than the one tested would demonstrate a different activity. Because the PTO "has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention" and such a basis is lacking here, the claimed invention is enabled. Indeed, the activity of all NTPs would be expected to be similar based on its similar structure and activity in other contexts.

6. Quantity of Experimentation

One of skill in the art could make and use the invention using only routine experimentation. Indeed, the preparation methods and screening assays needed to practice the full scope of the invention are known in the art and described in the specification. For example, NTP conjugates can also be made using only routine experimentation, as discussed above. Thus, a skilled artisan need only engage in routine experimentation to practice the full scope of the claimed invention.

7. Conclusion

One of skill in the art could practice the claimed invention without undue experimentation. Indeed, the specification supplements the prior art by providing extensive guidance to make and use the claimed invention. The working examples verify the teachings of the specification. Thus, one of skill in the art need only engage in routine experimentation to teach the full scope of the claimed invention. While the biological sciences are generally regarded as unpredictable, the experimentation needed is not particularly unpredictable. Accordingly, the specification enables the claimed invention.

For at least these reasons, Applicant respectfully requests reconsideration and withdrawal of this ground of rejection.

B. Claims 17-19, 21, 22, 39-42 and 44-45

Claims 17-19, 21, 22, 39-42 and 44-45 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. According to the Office Action, "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Office Action at 12. Applicant respectfully traverses this ground of rejection.

The specification contains a complete description of the invention of claims 17-19, 21, 22, 39-42 and 44-45 sufficient to allow one of skill in the art to make and use the claimed invention without undue experimentation for the same reason discussed above in Section V(A). In addition, the enablement of the claimed invention is further discussed below with reference to the factors articulated in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

1. Nature of Invention & Breadth of Claims

Claim 17 is dependent on claim 1 and recites that "the NTP is conjugated, linked, or bound to a molecule selected from the group consisting of an antibody, antibody fragment, and an antibody-like binding molecule, wherein said molecule has a higher affinity for binding to a tumor or other target than binding to other cells." The remaining claims further define the claimed invention, and state, for example, that "the composition is cleaved at or near the site(s) of the tumor or other unwanted cells by a tumor- or site-specific enzyme or protease or by an antibody conjugate that targets tumor or other unwanted cells and so releases the NTP."

Conditions "requiring removal or destruction of cells," NTPs, and the formulation of different dosage forms depending on the particular route of administration are known in the art and discussed in the specification, as discussed above.

2. Level of Ordinary Skill & Predictability in the Art

The biological sciences have been characterized as unpredictable, as compared to other technology areas, such as mechanical engineering and electronics. However, the level of ordinary skill in the art is very high with one of ordinary skill in the art typically having an advanced degree and industry experience.

In addition, certain areas of biological science are more predictable than others. For example, the production of biologically active fragments, variants, and derivatives is predictable based on the knowledge of conservative amino acid substitutions (*see e.g.*, pg. 1-1, Tables 1 and 2) and the availability of routine screening methods (*see* examples). Similarly, methods of making antibodies and forming cleavable linkages are well-known in the art and can be made routinely.

3. The State of the Prior Art & Guidance Provided By The Specification

The prior art contains extensive teachings of different forms of NTP, conditions requiring destruction or removal or cells, and methods of formulating and administering NTP. In addition, the prior art teaches how to form conjugates, such as active agent conjugated to an antibody or some other macromolecule. The following articles are representative of such teachings:

(1) Zhou *et al.*, ACTA PHARMACOL SIN 22(8):761-764 (2001);

(2) Ohya *et al.*, BIOMACROMOLECULES 2(3):927-933 (2001);

(3) Dowell *et al.*, J CLIN PHARMACOL 41(11):1206-1214 (2001);

(4) Shirota *et al.*, J PHARMACOL EXP THER. 299(2):459-67 (2001);

(5) Antczak *et al.*, BIOORG MED CHEM 9(11):2843-48 (2001);

(6) Bradley *et al.*, CLIN CANCER RES. 7(10):3229-38 (2001);

(7) Schaschke *et al.*, BIOORG MED CHEM LETT. 10(7):677-80 (2000);

(8) Shiah *et al.*, CLIN CANCER RES. 6(3):1008-15 (2000);

(9) Kratz *et al.*, CRIT REV THER DRUG CARRIER SYST. 16(3):245-88 (1999); and

(10) Sawa *et al.*, CANCER RES 60(3):666-71 (1999).

Thus, the specification need not describe specific NTP conjugates because a "patent need not teach, and preferably omits, what is well known in the art." MPEP § 2164.01.

The Office Action contends that "the specification fails to teach how to make any NTP conjugates where the activity of NTPs is shut down or inhibited during delivery and turned on only at site of a tumor or unwanted cells." Office Action at 18. However, the specification need not enable such a feature because such a feature is not claimed nor is it required to use the claimed invention. Chemotherapeutic agents that are toxic to tissue other than just tumor tissue are routinely administered both locally or systemically. If systemically administered, they can be delivered preferentially to the site of the tumor, such as by using a tumor-specific molecule. The NTP can be administered in the same way to practice the claimed invention. Thus, the NTP does not need to be "shut down" to practice the claimed invention.

4. Working Examples

The teachings of the specification are verified by the working examples. Example 1 demonstrated that an NTP was cytotoxic on glioma and neuroblastoma cells. The results demonstrated that "[s]ignificant cytotoxic effects on glioma and neuroblastoma cells" could be observed at 24 and 96 hours (pg. 45). Example 2 "was to determine the effect of NTP on tissue at sites of injection." Again, "[i]njection of AD7C-NTP in all examples produced abundant acute necrosis of tissues at the injection sites" (pg. 45). Finally, Example 3 "was to determine

the effect of NTP on different human and non-human origin tumors." The experiment confirmed that "there was significant necrosis" in "all cases tested" (pg. 46).

The Office Action states that "no working example is provided for a method of treating any conditions by any NTP conjugates." Office Action at 18. However, the examples provided are consistent in their results. Regardless of the type of tissue or its origin, the NTP induced acute necrosis. Moreover, there is no evidence or explanation to suggest that NTP conjugates would demonstrate a different activity. Indeed, conjugates are routinely made to deliver an agent to a specific location or to a particular class of cells. Because the PTO "has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention" and such a basis is lacking here, the claimed invention is enabled.

5. Quantity of Experimentation

One of skill in the art could make and use the invention using only routine experimentation. Indeed, NTP conjugates can be made using routine methods. These conjugates can be formed using cleavable linkages and antibodies, such as those that are well-known in the art. By conjugating NTP to molecules to molecules with an affinity for the cells requiring destruction, for example, the NTP can be administered locally to the cells. Mere routine experimentation is needed to make such conjugates and screen them for effectiveness. Thus, a skilled artisan need only engage in routine experimentation to practice the full scope of the claimed invention.

6. Conclusion

One of skill in the art could practice the claimed invention without undue experimentation. Indeed, the specification supplements the prior art by providing extensive guidance to make and use the claimed invention. The working examples verify the teachings of the specification. Thus, one of skill in the art need only engage in routine experimentation to teach the full scope of the claimed invention. While the biological sciences are generally regarded as unpredictable, the experimentation needed is not particularly unpredictable. Accordingly, the specification enables the claimed invention.

For at least these reasons, Applicant respectfully requests reconsideration and withdrawal of this ground of rejection.

VI. Claim Rejections – 35 U.S.C. § 112, First Paragraph – Written Description

A. Claims 17-19, 21, 22, 39-42, and 44-45

Claims 17-19, 21, 22, 39-42, and 44-45 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. According to

the Office Action, "[t]here is a lack of a written description regarding a protein, a molecule, dendrimers, fullerenes, synthetic molecules, polymers, macromolecules, antibody-like molecules' and 'tumor- or site-specific enzyme or protease or antibody conjugate'." Office Action at 19. Applicant respectfully traverses this ground of rejection.

Claims 17-19, 21, 22, 39-42, and 44-45 are original claims, and "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." MPEP § 2163(I)(A). The presumption cannot be rebutted here because the specification contains a description of the claimed invention sufficient to demonstrate possession of the claimed invention to one of ordinary skill in the art. Indeed, the specification describes the preparation of NTP conjugates, and proteins, molecules, dendrimers, fullerenes, polymers, macromolecules, antibodies, and antibody-like molecules suitable for use to make NTP conjugates are well known in the art, as discussed above in Section V(A). Accordingly, the specification contains a description of the claimed invention sufficient to demonstrate possession of the claimed invention to a skilled artisan.

The Office Action states that the description is lacking because the compounds themselves must be defined in greater detail. As support for this position, the Office Action cites case law including *The Regents of the University of California v. Eli Lilly*, 43 USPQ.2d 1398 (Fed. Cir. 1997).

However, *Lilly* and the other cases cited are inapposite to the present case. The cited cases deal primarily with claims to DNA molecules or claims to compounds that were not known in the prior art. That is not the case here. Instead, species of the compounds deemed lacking support in the Office Action are widely known in the art. For example, polymers and antibodies for forming conjugates, such as tumor-specific drug conjugates, are known in the art, as evinced above in Section V(A) by citation to references (1)-(10). *Amgen Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1332 (Fed. Cir. 2003) considered a similar situation. *Amgen* distinguished *Lilly* and its progeny by noting that "the claim terms at issue here are not new or unknown biological

materials that ordinarily skilled artisans would easily miscomprehend." *Amgen*, 314 F.3d at 1332. Thus, the claims were held to be supported by the written description despite the lack of an extensive description of species. Like the claim terms at issue in *Amgen*, the present terms deemed objectionable in the Office Action are known in the art and need not be defined the with same specificity as previously unknown compounds. Thus, the claims are supported b the specification.

For at least these reasons, Applicant respectfully requests reconsideration and withdrawal of this ground of rejection.

B. Claims 23-29, 31, and 39-45

Claims 23-29, 31, and 39-45 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. According to the Office Action, "[t]here is a lack of a written description regarding the structure and function of the fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers of the SEQ ID Nos. 2-9, neural pancreatic thread protein and pancreatic thread protein." Office Action at 22. Applicant respectfully traverses this ground of rejection.

The specification contains an extensive description of NTPs, including a variety of specific sequences and references to scientific literature describing NTP (*see e.g.*, pgs. 9-11). For example, Figures 1-9 each list an example of a specific NTP. This description is supplemented by an entire section describing the preparation of NTP, including fragments, homologs, variants, derivatives, peptide mimetics, reverse-D peptides, and enantiomers of NTP (pgs. 19-32). The preparation of modified forms of NTP is also defined with reference to scientific references to further assist one of skill in the art (*id.*; pgs. 11-18). For example, the specification describes peptide mimetics and cites to scientific references, which describe in greater detail the preparation of peptide mimetics.

Based on this extensive description, one of skill in the art would readily understand Applicant to be in possession of the claimed invention. Indeed, the description of specific NTP species coupled with detailed descriptions methodologies evinces possession of the claimed invention. For example, a skilled artisan could compare the specific sequences to determine conserved regions and based on these results make conservative or non-conservative amino acid substitutions, which are described in Tables I and II, to form modified forms of NTP. Fragments could also be routinely made and screened for biological activity using the methods defined in the specification, including the working examples. Accordingly, the claims are fully supported by the application as-filed.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

VII. Double Patenting

A. Rejection Over U.S. Patent No. 6,924,266

Claims 1-7 and 9 stand rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 4-7 of U.S. Patent No. 6,924,266. According to the Office Action, "[a]though the conflicting claims are not identical, they are not patentably distinct from each other." Office Action at 25. Applicant respectfully traverses this ground of rejection.

The '266 patent claims a "method of treating a benign or malignant tumor in a mammal comprising local administration of a therapeutically effective amount" of one of the specifically defined NTPs recited in claim 1. Based on this disclosure, one of skill in the art could not extrapolate that NTPs in general could be used to treat "a condition in a patient requiring removal or destruction of cells," as claimed. Indeed, agents for the treatment of tumors do not necessarily treat all conditions requiring removal or destruction of cells. Applicant notes that the disclosure of the '266 patent cannot be used to find the presently claimed invention obvious over the claims

of the '266 patent. Thus, Applicant respectfully requests reconsideration and withdrawal of this ground of rejection.

B. Rejection Over Co-Pending Applications

Claims 1-7 and 9 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over "claims 12-16 and 18 of copending Application No. 10/294,891 and claims 9-13 and 15 of copending Application No. 10/920,313." Office Action at 27.

Applicant notes the provisional nature of this rejection and will address the rejection on the merits if it ever matures into a non-provisional rejection.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date May 8, 2006

By Michele M Simkin

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

Michele M. Simkin
Attorney for Applicant
Registration No. 34,717